Received: 3 July 2018 | Revised: 16 April 2019 | Accepted: 29 April 2019

DOI: 10.1111/bcp.13986

ORIGINAL ARTICLE

Body of evidence and approaches applied in the clinical development programme of fixed-dose combinations in the European Union from 2010 to 2016

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Funding information
Novo Nordisk

Aims: To provide insights into the clinical development pathway for fixed-dose combinations (FDCs), to consider strategies, and to elucidate the path to approval by assessing the body of evidence, as summarized in the European Public Assessment Reports.

Methods: The main resource was the European Public Assessment Reports for 36 FDCs, which included 239 clinical trials with 157 514 patients. The analyses focused on how prior knowledge of the active substances or combination, use of pharmacokinetic–pharmacodynamic modelling, and clinical trial design choice impact the size and strategy of the clinical development programme.

Results: FDC products primarily comprised 2 previously approved components (21/36, 71%) and had only 1 approved combination (21/36, 71%). Utilizing previously approved active substances resulted in fewer clinical trials, arms and patients, but FDC doses studied in the clinical development programme. Furthermore, dose-finding trials were performed for less than half of FDCs consisting of 2 previously approved active substances. The standard approach to demonstrate contribution of active substances was through a factorial or single combination study. Finally, the use of pharmacokinetic modelling showed a significant decrease in the number of FDC doses studied.

Conclusions: The field of FDCs seems to be on the rise, utilizing new molecular entities, prior knowledge and re-profiling drugs. However, a way to move FDC development forward might be through new regulatory and scientific paradigms, in which it is encouraged to utilize model-based approaches to develop FDCs with multiple dose levels and dose ratios for exposure-based treatment that will enable personalization.

KEYWORDS

clinical development, fixed-dose combination, market authorization, PK-PD modelling, regulatory science

1 | INTRODUCTION

Fixed dose-combination (FDC) products, a subset of combination therapies, contain a fixed ratio of 2 or more active ingredients with distinct modes of action formulated into a single dosage form. FDC products contribute to treatment regimens with unique advantages compared to conventional single agent therapies by providing an enhanced clinical efficacy or safety profile, improved patient compliance and convenience, or opportunities for development of novel treatment entities through synergistic action of the components.[1,2] The understanding of many diseases as containing numerous pathways responsible for the disease has been essential in driving the development of combination therapies, which are capable of targeting these complex networks at multiple sites simultaneously.[3] This is in particular the case for the treatment of infectious diseases e.g. human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome, tuberculosis and malaria.[4,5] Lastly, the synergistic action of combination therapy has proved instrumental in circumventing resistance when treating cancer[6,7] as well as in combating multidrug-resistant microbial infections.[8]

From a regulatory perspective, FDC products are subject to separate regulations by the US Food and Drug Administration,[9] European Medicines Agency (EMA)[10,11] and the World Health Organization.[4] Historically, these recommendations were introduced to ensure the rationale for combining 2 or more active ingredients, as irrational combinations may potentially expose patients to risks of adverse reactions while providing no added value to the treatment.[12] The current EMA guideline was adopted in 2017,[11] replacing the previous version from 2009.[10] The present study focuses on FDCs approved from 2010–2016 to cover the period the previous guideline was in effect. Key requirements from the 2009 guideline are outlined here: (i) justification of the potential advantage of a FDC through either improved benefit/risk or a simplification of therapy; (ii) each substance must have a documented therapeutic contribution within the combination; and (iii) indication of the FDC should be classified as first-line, second-line or substitution therapy. Depending on the potential advantage, substances and indication, the appropriate data and clinical development needed to fulfil the requirements varies considerably. Furthermore, the EMA distinguishes between the documentation needed to support pharmacokinetics (PK) and pharmacodynamics (PD) based on existing documentation and previous use of the active substances or the combination.

One way of adhering to the guideline requirements is by using drug development tools (DDTs). Several DDTs are well-defined, including biomarkers, clinical outcome assessment, and animal models.[13] Another important DDT is PK-PD modelling, which enables model-informed drug development (MIDD).[14,15] The advantages of successfully applied MIDD is established in many different aspects and phases of the drug development process through, amongst others, improved biomarker selection, characterization of PK parameters, evidence generation for regulatory approval, and early input into pharmaco-economic assessment.[15] The theoretical application of PK-PD modelling in FDC development has been demonstrated in several publications[16,17] and various combination models have been developed, attempting to capture the combined effect of 2 or more compounds given additive, synergistic or antagonistic assumptions.[17-19] Indeed, based on the literature, these tools could readily be applied; however, to our knowledge no studies have investigated whether they are in fact employed in the clinical development of FDCs.

Marketing Authorization Applications (MAAs) for FDCs approved by EMA have previously been subject to in-depth analysis, focusing on topics such as reasoning for authorization.[20] The aim of this study was to provide insights into the clinical development pathway for FDCs, consider strategies, and to elucidate the path to approval by assessing the body of evidence submitted with MAAs, as summarized in the European Public Assessment Reports (EPAR). The objectives were: (i) to summarize the body of clinical evidence focusing on the number of patients, arms, clinical trials, and FDC doses studied in the clinical development programmes for FDCs and evaluate the difference in evidence between clinical trials phases; (ii) to assess the impact of how prior knowledge affect the clinical development programme, based on how substance status (approved drug [AD] or new molecular entity [NME]) influence the programme size (patients, arms, clinical trials, and FDC doses studied) and whether dose-finding trials were performed; (iii) to consider the clinical trial design choice in view of the fact that the standard approach for demonstrating the

What is already known about this subject

- Marketing Authorization Applications for fixed-dose combinations (FDCs) approved by European Medicines Agency have previously been subject to in-depth analysis, focusing on topics such as reasoning for authorization.
- Based on the literature, pharmacokinetic (PK) and pharmacodynamic modelling could readily be applied to the clinical development of FDCs; however, little evidence exists to determine whether it is in fact employed.

What this study adds

- Utilizing previously approved active substances resulted in fewer clinical trials, arms and patients, but doses studied in the clinical development programme. Dose-finding trials were performed for less than half of FDCs consisting of 2 previously approved active substances.
- PK or PK–pharmacodynamic modelling was applied in only 58% of clinical development programmes. PK modelling significantly decreased the number of doses studied, indicating that firmly understanding the kinetics of the drug candidate is essential for selecting the right doses.
- With increased focus on personalized medicine, maintaining the rise in FDCs will require new strategies to support development of FDCs with multiple doses and dose ratios.

contribution of each active substance is generally accepted as being a factorial design study[16]; and (iv) to analyse the use of PK-PD modelling and how it affects the clinical development programme for FDCs as well as how FDCs fit in an era of personalized medicines.

2 | METHODS

The main resource for this study were the EPARs, which are publicly available online. The data presented here are taken from these reports; however, if information was missing or if certain details were unclear, a search was conducted using 1 or more of the following databases: https://www.clinicaltrials.gov, https://www.clinicaltrialsregister.eu/, https://www.gsk-clinicalstudyregister.com/, using the clinical trial identifier, sponsor and/or drug name as the search terms.

The present study included MAAs with authorization date from January 2010 to December 2016 and considered only the applications in which the drug product contained 2 active substances. Neither products that were refused approval by the Committee for Medicinal Products for Human Use nor products that were withdrawn after market authorization were considered. Additionally, products that were considered either generic, biosimilar, vaccine or orphan products were considered to be outside the scope of this review and were therefore excluded, Figure 1. This led to a final pool of 55 FDCs for analysis from which 19 were excluded (criteria outlined in Supporting information Appendix S1) e.g. applications, which were submitted as informed consent application in accordance with Article 10c of Directive 2001/83/EC, were excluded since the supporting data for these applications is essentially the same as for the reference product.

From the EPAR, the *new active substance status* was screened to assess the claim of new active substance status for 0, 1 or 2 components, defined as AD and NME and the combinations thereof (AD +AD, AD+NME, and NME + NME). The *clinical aspects*, *clinical efficacy* and *clinical safety* sections were reviewed for number of patients, clinical trial characteristics, dose selection process and use of modelling. Modelling was divided into 2 groups: use of only PK modelling, and the use of both PK and PD modelling. For extracting data regarding anatomical therapeutic chemical (ATC) codes and approved doses of FDC the associated *Product information* and *Authorized presentations* documents were used. Specifically, for analysis of the trial data, only studies that were performed until the marketing authorization date were considered, thus postmarketing is outside the scope of the present study. Extension trials were considered part of the study only if new patients were enrolled in the trial. The design used in the dose-finding trial or, if no dose finding was performed, the main pivotal trial (as defined or evaluated from the EPARs *main studies* section) was extracted. Classification of design was done according to the following criteria: (i) factorial approach: 2 or more combinations with different ratio between components; (ii) ray approach: 2 or more combinations with the same ratio between components; (iii) single combination approach: only 1 combination tested. One researcher (A.N.) extracted all data and a second (T.M.L.) was consulted if doubt regarding inclusion of a study occurred. The presented data are based on publicly available information.

2.1 | Statistics and analysis

Statistical analyses of the objectives were performed to provide evidence-based quantification of how prior knowledge, use of PK-PD modelling, and choice of clinical trial design influence programme size as well as how the body of evidence is distributed between clinical trial phases. Furthermore, ATC code and number of approved FDC doses were included in the model to control for the difference in requirements between disease areas and number of approved FDC doses, respectively. Statistical analyses were done using R

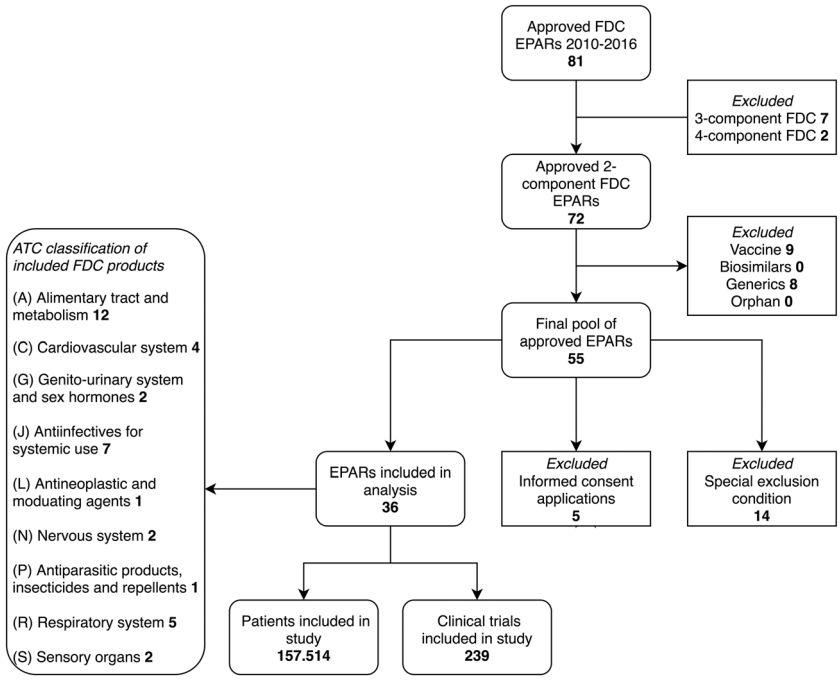

FIGURE 1 Flowchart showing the identification of excluded and included European Public Assessment Reports (EPARs) in the present study. Distribution of the included EPARs in the anatomical therapeutic chemical (ATC) classification system is shown to the left. The condition for exclusion of other applications are outlined in Supporting information Appendix S1. FDC, fixed-dose combination

3.4.3[21] and the R package *geepack* .[22] A generalized linear model with a log-link and Poisson error distribution was employed for the 4 different response variables (number of patients, arms, clinical trials and FDC doses studied). For each outcome, 2 models were formulated with 5 predictor variables: clinical trial phase; substance status; PK-PD modelling; number of approved FDC doses; and either ATC code or design. ATC code and design are not in the same model due to collinearity. In addition, indication (first-line, second-line or substitution therapy) is not included as it shared collinearity with ATC code. Robust standard errors of estimates were computed by the independence working GEE approach to account for trial heterogeneity. Effects of clinical trial phase, substance status, and PK-PD modelling controlled for ATC code and number of approved FDC doses are derived from a multiple regression (ATC model), while the effect of design controlled for clinical trial phase, substance status, PK-PD modelling and number of approved FDC doses is derived from another multiple regression (design model).

The graphical representation of the data was performed using the *ggplot2* R-package.[23] Plots present the crude unadjusted values from the data and as such does not 1:1 match the tables, while the adjusted analysis was used to assess statistical significance.

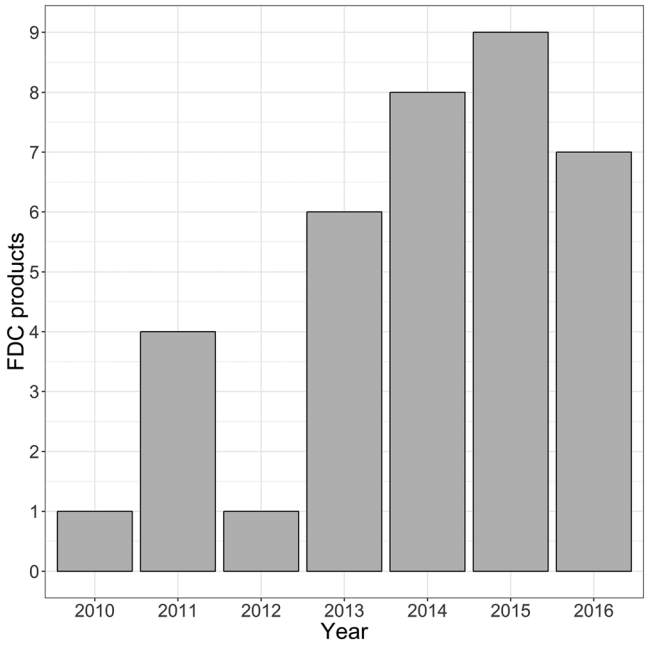

FIGURE 2 Overview of the number of fixed-dose combination (FDC) products approved per year by the European Medicines Agency from 2010–2016

3 | RESULTS

We identified 36 FDC products approved in the period from January 2010 until December 2016, which matched the selection criteria for the present study. An overall increase in approvals by the EMA for FDCs is observed during this period, Figure 2. Analysing the trend using linear regression shows that this overall increase has a significant slope (P = .02). A detailed overview showing the full ATC codes, active ingredients, marketing authorization holders and authorization dates of these products are listed in Supporting information Appendix S2. In addition, a graphical summary of the variables of interest in the study is provided in Supporting information Appendix S3.

3.1 | FDC disease areas and body of clinical evidence

The major group of 12 FDCs (33%) are classified in (ATC A) *alimentary tract and metabolism* and comprise a group of compounds mainly indicated for the treatment of type-2 diabetes (10/12, 83%). Within this group, a first-line medication for the treatment of type-2 diabetes, metformin, was combined with previously ADs and NMEs in 5 instances. In most cases, FDCs have been approved for 1 or 2 doses; however, 5 FDC products had 4 approved doses (Table 1). This group consisted of 3 FDC products classified for the alimentary tract and metabolism (ATC A), 1 for the cardiovascular system (ATC C) and 1 for the nervous system (ATC N). All the medicines within the metabolic group had diabetes as indication and 2 of them included metformin, which is often administered at many doses. For the cardiovascular FDC product telmisartan/amlodipine, 9 FDC doses were studied during the clinical development process. The nervous system

TABLE 1 Overview of fixed-dose combination (FDC) characteristics

	Category	Number of FDC products (n = 36)
Approved combination doses	1 dose	21
	2 doses	9
	3 doses	1
	4 doses	5
Substance status	AD+AD	21
	AD+NME	13
	NME + NME	2
Trial design	Ray	3
	Factorial	16
	Single combination	17
Use of PK-PD modelling	No modelling	15
	PK modelling	13
	PK-PD modelling	8
	Category	**Number of FDC components (n = 72)**
ATC code levels of component in common with parent FDC	0	3
	1	1
	2	16
	3	23
	4	11
	None	18

AD+AD, FDC composed of 2 previously approved drugs; AD+NME, approved drug combined with a new molecular entity; NME + NME, combination of 2 new molecular entities; Trial design, trial design used in the dose finding trial or, in case no dose finding was performed, the main pivotal trial; PK, pharmacokinetic; PD, pharmacodynamic; ATC, anatomical therapeutic chemical

medication had Parkinson's disease as indication and consisted of carbidopa and levodopa.

To assess whether FDC components predominantly are used for the same indication as when they were used for monotherapy, the ATC codes of the FDC components were compared to that of their respective parent FDC and evaluated for how many ATC levels were in common. One level corresponded to the anatomical group, 2 levels to the therapeutic subgroup, 3 levels to the pharmacological subgroup and 4 levels to the chemical subgroup. A small group (4/72, 6%) of components were found to have either 0 or 1 ATC code level in common with their parent FDC and is therefore used either in a new anatomical area or for a different therapeutic purpose from their parent compound. A much larger group (50/72, 69%) have 2, 3 or 4 levels in common with the parent FDC, which indicates a change in pharmacological subgroup, chemical subgroup or that the component and parent is the same at every level, respectively. The *None* group represents components with no ATC code and comprises the NMEs and piperaquine (Eurartesim FDC), an antimalarial drug discovered in the 1960s.

An overview of the body of clinical evidence, which was performed by the sponsors in phase 2 and phase 3 clinical trials, is shown in Figure 3 and analysed using the ATC model, Table 2A. In Figure 3A the distribution of the total number of clinical trials performed in each EPAR is shown. A significant difference in the distribution between phases is observed ($P < .001$), with phase 2 distribution polarizing towards 0–2 trials performed and the phase 3 distribution centring around 3–4 clinical trials performed. Likewise, the distribution for the total number of arms has a polarization towards 0 in phase 2 and slightly higher in phase 3, centring around 5–10 arms; however, this difference in distribution is not statistically significant, Figure 3B. The distribution of total number of patients ranges from 27–4500 in phase 2 trials with the majority being in the 27–1500 range, Figure 3C. In comparison, the number of included patients in phase 3 display smooth distribution between 556–13500 patients. Analysing

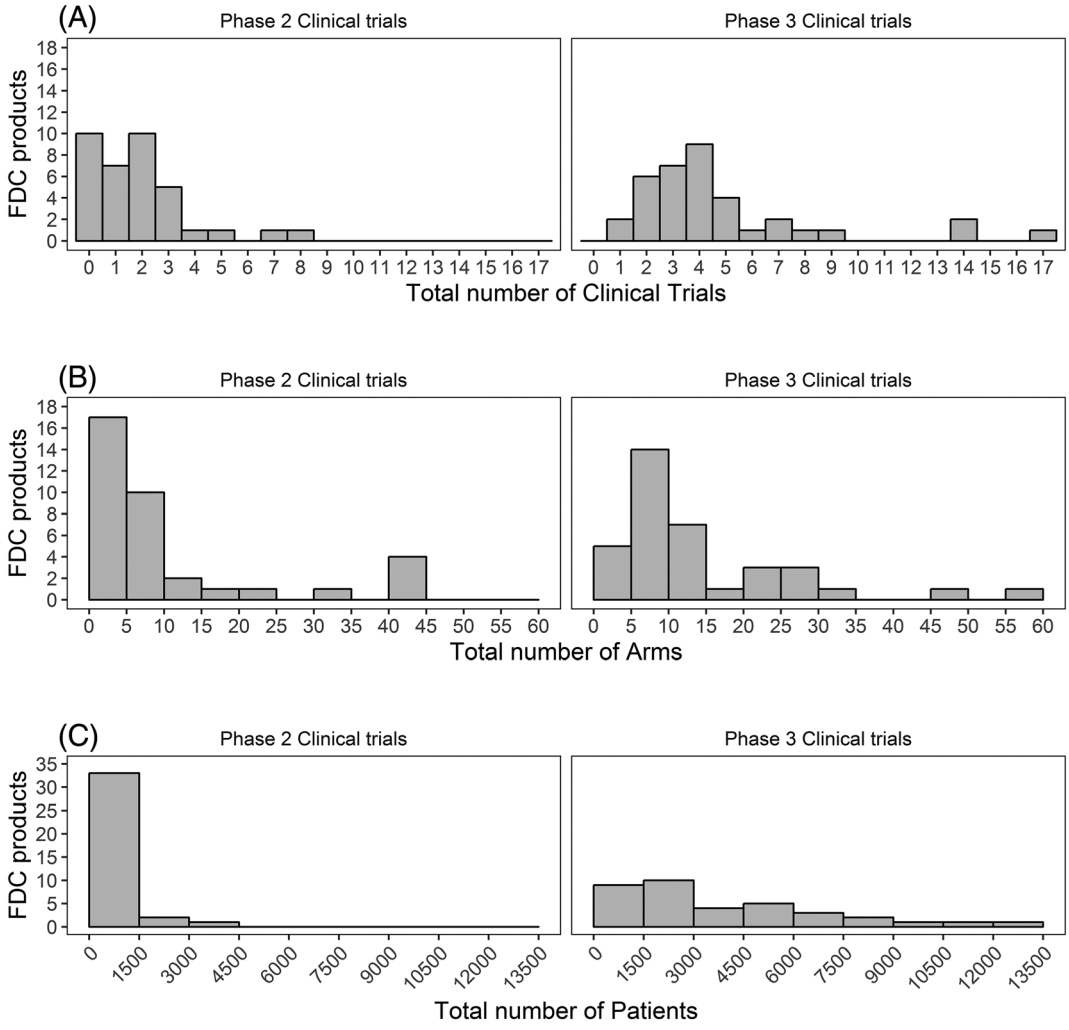

FIGURE 3 Histograms displaying the distribution of the total number of (a) clinical trials, (B) arms and (C) patients studied before the approval of fixed-dose combinations (FDCs) by European Medicines Agency. The distributions are divided into panels by clinical trial phase, phase 2 (left) and phase 3 (right). A significant difference in the distribution was observed between phase 2 and phase 3 for clinical trials ($P < .001$) and patients ($P < .001$) when adjusting for anatomical therapeutic chemical code, substance status, modelling and number of approved FDC doses, but not for the distribution of arms ($P = .081$)

TABLE 2 Anatomical therapeutic chemical model: *P*-values and estimates

		Response variables											
		Patients			Arms			Trials			FDC doses studied		
Reference variables	Coefficients	Estimate	Std. error	*P*-value	Estimate	Std. error	*P*-value	Estimate	Std. error	*P*-value	Estimate	Std. error	*P*-value
A – Anatomical therapeutic chemical model													
Phase 2	Phase 3	**2.032**	**0.206**	**<.001**	0.374	0.214	.081	**0.964**	**0.164**	**<.001**	0.236	0.212	.265
AD+AD	AD+NME	**0.517**	**0.221**	**.019**	**0.650**	**0.237**	**.006**	**0.753**	**0.274**	**.006**	0.000	0.134	.999
	NME + NME	0.385	0.200	.054	**1.077**	**0.279**	**<.001**	**0.951**	**0.225**	**<.001**	0.284	0.344	.410
No modelling	PK modelling	0.239	0.249	.336	0.151	0.285	.596	0.150	0.219	.495	**−0.648**	**0.309**	**.036**
	PK-PD modelling	−0.108	0.250	.667	0.016	0.241	.946	−0.157	0.262	.550	0.099	0.130	.443
B – Design model													
Factorial	Single comb.	−0.478	0.287	.096	−0.408	0.266	.125	−0.224	0.229	.328	**−0.828**	**0.179**	**<.001**
	Ray	**−1.407**	**0.327**	**<.001**	**−0.851**	**0.228**	**<.001**	−0.369	0.204	.070	−0.212	0.133	.110

Reference variable, variable contained in the intercept; Coefficients, variables that is compared to the respective reference variable; AD+AD, FDC composed of 2 previously approved drugs; AD+NME, approved drug combined with a new molecular entity; NME + NME, combination of 2 new molecular entities; Trial design, trial design used in the dose finding trial or, in case no dose finding was performed, the trial design from the main pivotal trial; PK, pharmacokinetic; PD, pharmacodynamic; bold values, $P < .05$

the number of patients shows a significant difference between the phase 2 and phase 3 distributions ($P < .001$).

3.2 | Impact of prior knowledge on the clinical development programme

The majority of the FDC products in the present study consist of 2 previously approved components as shown in Table 1. However, in 13 cases, the sponsor has opted to apply for approval of 1 component as a new active substance in conjunction with applying for approval of the FDC product. Additionally, in 2 cases, both components have been considered new active substances. The impact of this measure on the size of the clinical development programme, with respect to patients, arms, clinical trials and FDC doses studied, is shown in Figure 4. All data in this figure were analysed using the ATC model, Table 2A. For clinical trials, there are significantly more trials conducted for AD +NME and NME + NME compared to AD+AD, Figure 4A. A similarly significant result is observed for the effect of AD+NME and NME + NME on arms, when compared to AD+AD. For patients, only AD+NME had a significant effect compared to AD+AD. Additionally, when comparing the AD+NME and NME + NME groups for clinical trials, arms and patients there is no statistical difference (data not shown). Lastly, no statistically significant difference is seen between the groups for FDC doses studied.

In addition to the impact on the programme size, it was investigated how prior knowledge affect 1 approach in the clinical development, namely whether dose-finding studies were performed. Figure 4B shows how often sponsors performed dose-finding studies as part of their clinical development programme, stratified by the substance status of the FDC. For the AD+AD group more than half (12/21, 57%) of the assessment reports include no dose-finding trial, while for the 2 other groups, which include at least 1 NME, a dose-finding trial was performed in all cases.

3.3 | Demonstrating contribution of active substances to the effect

Information gathered in the dose-finding trial or in the main pivotal trial is crucial to the goal of demonstrating superiority of the FDC over the individual components. Thus, using an optimal design is vital in reaching this goal. As seen from Table 1, slightly less than half (16/36, 44%) made use of the factorial design in their dose-finding/pivotal trial, the design considered to be the standard approach for demonstrating contribution of components. Few sponsors used ray design (3/36, 8%), and finally the *single combination* design group was used 17/36 (47%) times, showing that for almost half of the FDC authorizations, only a single combination was studied to get approval. Furthermore, it was investigated how the choice of clinical trial design affected the size of each clinical development programme, with respect to patients, arms, clinical trials and FDC doses studied, using the design model, Table 2B. This was done to provide a comparison of the strategies employed by the sponsors. When comparing factorial design to ray design, a significant decrease in the total number of patients analysed ($P < .001$) was seen, Figure 5A. Similarly, the total number of arms ($P < .001$) decreased; however, the effect on number of trials and FDC doses studied was not significant. There is no significant difference in the number of patients, arms or clinical trials analysed for factorial design and the single combination design group; however, naturally, there was a decrease in the number of FDC doses studied ($P < .001$), Table 2B.

Moreover, it was investigated whether the sponsors employed the use of PK and/or PD modelling as part of the clinical development programme. More than half (21/36, 58%) of the dossiers described the use of various models as part of the development process, with 13 focussing solely on PK and 8 including both PK and PD modelling. The effects of performing PK or PK-PD modelling as part of the clinical development programme was evaluated with regards to patients, arms, clinical trials and FDC doses studied using the ATC model, Table 2A.

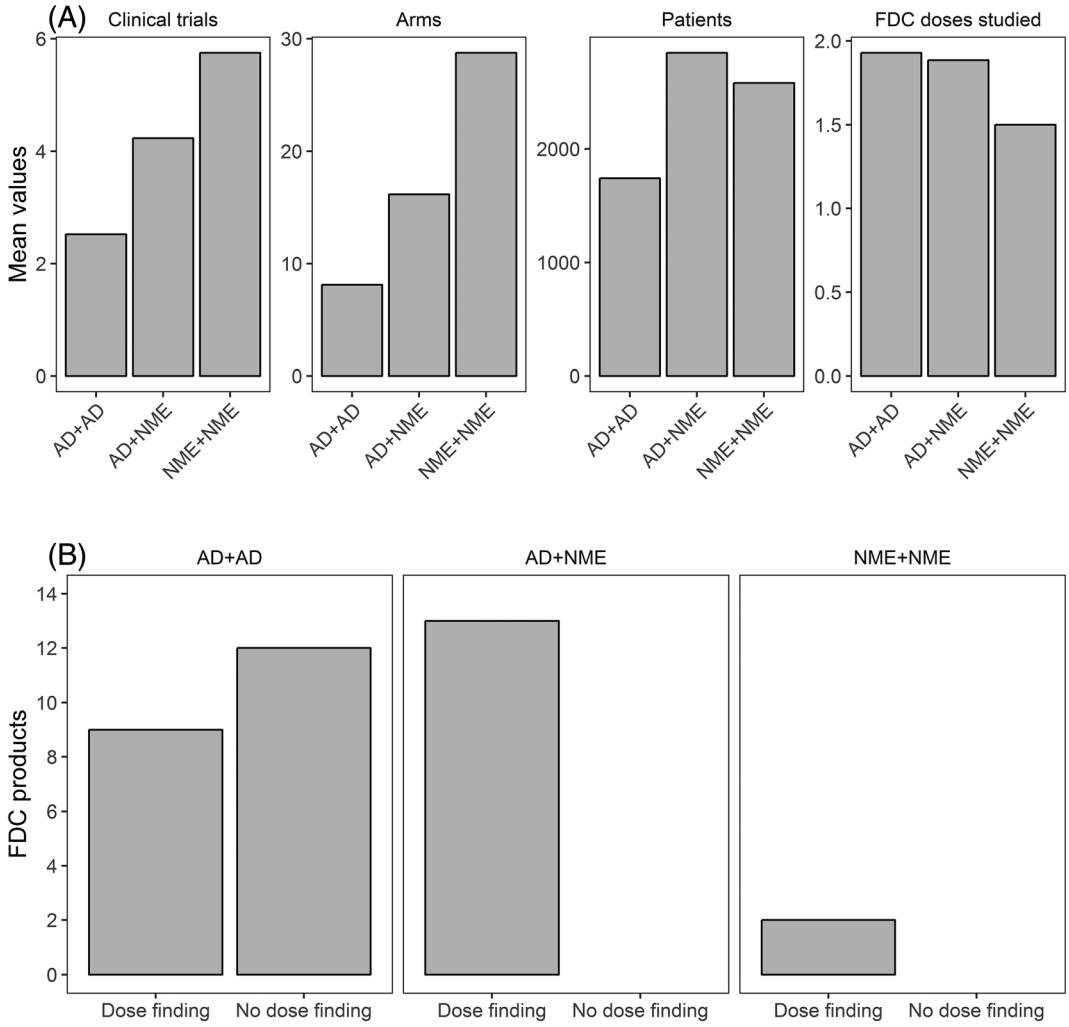

FIGURE 4 (A) Overview of the mean of clinical trials, arms, patients, and fixed-dose combination (FDC) doses studied before the approval of FDCs by the European Medicines Agency segmented by substance status. Significantly more clinical trials, arms and patients were examined for AD+NME ($P = .019$, $P = .006$, and $P = .006$, respectively) compared to AD+AD. For NME + NME significantly more clinical trials and arms, but not patients were examined ($P < .001$, $P < .001$, and $P = .054$, respectively) compared to AD+AD. Contrasting this, the effect of substance status on FDC doses studied was not observed. (B) Frequency of the performance of dose finding segmented by substance status. AD, approved drug; NME, new molecular entity

There was no significant effect of PK or PK-PD modelling on the number of patients, arms or clinical trials. However, when reviewing the effect of PK modelling on FDC doses studied, a significant decrease was observed compared to the no modelling group ($P = .036$), Figure 5B. For this category, the use of PK-PD modelling showed no difference compared to when no modelling was performed.

4 | DISCUSSION

4.1 | Limitations

The present study provides insights into the clinical development pathway for FDCs; however, some limitations to data collection and analysis should be considered. Importantly, studies that are to be performed as part of a conditional marketing authorization are not included in the analysis, as not all have been conducted yet. Furthermore, as the study included approvals from 2010–2016, some clinical trials will have begun before the 2009 guideline was instated. Finally, as FDC indication (first line, second line or substitution therapy) shared collinearity with ATC code, it could not be considered in the analysis. For the clinical trial design analysis, it should be underlined that the trial designs selected for the clinical development programmes were selected with a specific goal in mind. A goal that cannot necessarily be achieved using any other trial design. The design analysis has the inherent limitation of assuming that each design would be applicable for each clinical trial.

The PK-PD modelling analysis does not account for the different purposes of modelling, as the data available do not clearly describe the reason for employing it. Hence, we analysed the usage of modelling in a yes/no manner, which fails to capture the deeper reasoning behind using modelling and might cause the discrepancy in the

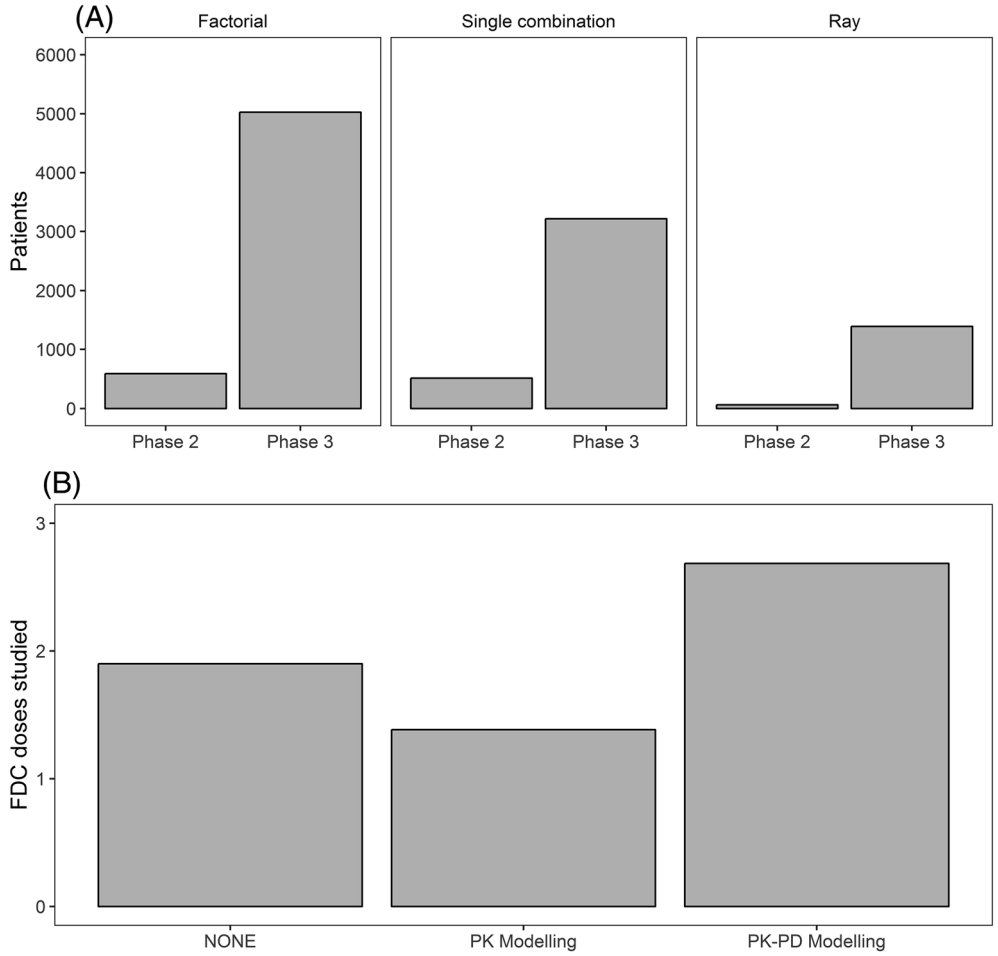

FIGURE 5 (A) Mean number of patients in phase 2 and phase 3 trials segmented by the clinical trial design of the dose finding study or main pivotal trial. A significantly lower total number of patients were analysed for ray design ($P < .001$) compared to factorial design using the design model, but not for single combination design ($P = .096$). (B) Mean number of fixed-dose combination (FDC) doses studied segmented by whether no modelling, pharmacokinetic (PK) modelling or PK-pharmacodynamic (PK-PD) modelling was performed. Significantly fewer FDC doses were studied when PK modelling ($P = .036$) was performed compared to no modelling (none), while no significant effect of PK-PD modelling was observed on the number of FDC doses studied

findings. Furthermore, there might still be a benefit of the modelling on parameters not considered here, such as better prediction of the optimal dose ratio in terms of the efficacy or safety profile.

4.2 | FDC landscape

Gaining approval for FDC products is a complex endeavour with a great degree of nuance depending on many factors, such as substance status, existing pool of information, and disease area. Despite this, there has been a significant increase in FDC approvals per year from 2010 to 2016.

One appeal of developing FDCs is the optimization of treatment within a therapeutic area. As a measure of this, we analysed the ATC levels for components and parent compound that were in common. Sharing 2, 3 or 4 ATC code levels was considered as components being used within the same indication, as they were for monotherapy. Another appeal is the re-profiling of compounds for new indications. Based on the same approach, components sharing 0 or 1 level of ATC code with their parent compound was considered as re-profiled. An example of this from the present study is Mysimba,[24] a combination of naltrexone and bupropion indicated for obesity. Bupropion has in this case been re-profiled as it is most commonly used in the treatment of depression and is therefore classified for the nervous system. Although the landscape for FDCs predominantly (50/72, 69%) consists of improvement within a therapeutic area, the small group (4/72, 6%) of re-profiling drugs represent an interesting opportunity as the development cost is greatly reduced and the success rate is markedly higher for re-profiled drugs.[25]

4.3 | Impact of prior knowledge on the clinical development programme

Substance status, as a measure of the amount of prior knowledge available to sponsors, was evaluated with respect to patients, arms, clinical trials and FDC doses studied in the clinical development

programme. The results showed that there was a clear relationship between the extent of prior knowledge and the number of patients, arms and trials involved. This corresponds well with the guideline allowing the extent of studies to be based on amount of existing documentation as well as previous use of the active substances or the combination. However, not , it was found that prior knowledge had no impact on the number of FDC doses studied that need to be studied for approval, as prior knowledge on the mono-components cannot be extrapolated to inform on effects of the combination.

Only 2 FDCs consisted of components that were both new active substances. The first of these is Zepatier, an FDC product composed of grazoprevir and elbasvir indicated for the treatment of hepatitis C. The second is Anoro, a combination of umeclidinium bromide and vilanterol trifenatate indicated for the treatment of chronic obstructive pulmonary disease. The majority of FDCs are AD+AD, hence FDCs are predominantly being evaluated clinically after the approval of the components as monotherapies, and thus the focus in FDC development is on clinical studies of the combination.

Dose-finding trials were skipped in 12 instances for FDCs composed of 2 previously ADs. An approach is described in the guidelines for FDCs when the doses *"...are identical to the doses used in the broad clinical setting and safety data generated with these doses are available..."*.[10] Given the disparity in the existing pool of data for AD+AD and AD+NME/NME + NME it makes sense to rely on information gathered when the individual components were investigated. However, although it presents an interesting strategy to FDC development, it should be considered that the trade-off could be a lost opportunity of finding more optimal doses or dose ratios, which could either lower the side effects or increase the efficacy.

4.4 | Demonstrating contribution of active substances to the effect

As outlined in the guidelines it is required to demonstrate contribution of the components. Analysis revealed that 44% employed the standard approach of factorial design to fulfil this requirement. The *single combination* was used slightly more with 47% and can technically be considered a subset of the factorial design using a simple AB, A and B design. This leaves only 8% exploring an alternative option, the ray design. Comparing the designs, we found that there is significantly lower number of patients involved in the clinical development programmes where ray design was selected compared to factorial design.

Considering FDCs in the light of personalized medicine presents obvious hurdles, as the apparent inability to adjust the dose ratio directly conflicts with the concept of personalization. However, in some cases, they can be seen as part of the same purpose - providing tailored care for each individual patient. Indeed, for the 15 products where multiple dose combinations were approved, it is possible to personalize the treatment. Conversely, for the majority (n = 21) of the FDCs where only 1 combination is approved, it indicates that the current FDCs on the market are not geared towards personalization.

To move FDCs forward in an era of personalized medicines it is paramount that each combination can be tailored to the individual. This becomes increasingly complex when considering special populations where dose personalization of a single component of the FDC would require that multiple dose ratios of the combination exist. Furthermore, demonstrating the contribution of components for an array of FDCs with multiple dose levels and dose ratios using a full factorial design would result in clinical trials of extraordinary size, creating a barrier for FDC development. While ray design presents an alternative to the factorial approach, it does not solve this issue. Alternative strategies to demonstrate contribution of components have been attempted using exposure–response analysis. However, this approach proved to have an inflated false positive rate due to the correlation between doses of the components.[16] Therefore, new efforts must be made to identify alternative approaches or tools to assist in determining the contribution of components, thereby partially enabling development of tailored treatment.

A way forward may be model-based adaptive optimal design (MBAOD) as shown in a recent study on dose finding in combination therapy within oncology.[26] MBAOD makes use of nonlinear mixed effect models and consist of a series of adaptive steps. The study population is divided into cohorts and after analysing each cohort, the information gathered is used in the model, thereby providing new information for the analysis of the subsequent cohorts. By gathering information in this manner, MBAOD has been shown to improve the efficiency of identifying the optimal dosing regimen for drug combinations and to allow for a stopping criterion that can result in smaller sample size requirements.[26]

4.5 | The future of FDCs

PK-PD modelling as a drug development tool can exploit the information gathered early on in the development process to guide the optimal dose selection and provide information regarding the expected effect size.[27] The size of the measured effect is paramount when designing the phase 3 clinical trials in order to ensure the right power in the studies. Therefore, it is surprising that only 58% of the EPARs report the use of PK or PK-PD modelling. In particular, PK-PD modelling is left unexplored with only 8 of the EPARs mentioning its use. An explanation for this could be that relatively rich sampling is required to perform a meaningful PK-PD analysis, which might also explain the apparent increase in FDC doses studied for the PK-PD modelling group. Employing PK modelling showed a significant decrease in the number of FDC doses studied, implying that firmly understanding the kinetics of the drug candidate is essential for selecting the right doses. PK or PK-PD modelling showed no effect on number of patients, arms or clinical trials, a result that seemingly conflicts with the established literature, where MIDD is described as a multipurpose tool capable of amongst others enable study design optimization, prediction and characterization of PK parameters, benefit/risk characterization, and dose selection.[15] The reason for this was discussed in the limitations.

The present study has focused on the later stages of development, specifically how innovative trial designs or PK-PD modelling could play an integral part of this development. While undeniably important, it is equally essential to consider the evidence arising in the earlier stages of development from nonclinical target identification to preclinical development and PK characterization. Understanding the PK profile, either through demonstrating bioequivalence or a full characterization is another guidance requirement and is integral in determining the optimal dose. Traditionally, optimal dose was based on dose–response analysis; however, due to variability in target populations a single dose does not correspond to a single effect across the population. Fully characterizing the PK profile through modelling facilitates an understanding of how several factors, e.g. weight, age or renal function, influence PK, thereby linking the dose to an expected exposure and enabling dosing based on exposure–response. Dosing based on the dose-exposure–response approach can be tailored to special populations, such as children, ethnic groups or obese patients, and is central in personalizing treatment.[28]

The advantages of firmly understanding the underlying exposure–response relationship of a drug combination, selecting the right biomarker, accurately determining the effect size, and designing flexible trials that can identify the best dosing regimen cannot be overstated. Using model-based approaches and methods to identify these factors is the core of MIDD and facilitates an improved development process. Given these advantages and the increased focus from the regulatory authorities on the use of model-based approaches, such as the EMA's reflection paper on the use of extrapolation[29] and coupled with the very limited application of model-based tools in FDC development shown in this study, it is evident that a shift towards model-based FDC development is essential.

In conclusion, the field of FDCs seems to be on the rise, utilizing NMEs, prior knowledge, and re-profiling drugs. However, to move FDC development forward, not only is a scientific paradigm needed, in which model-based methods and approaches such as MBAOD and MIDD are employed, but a new regulatory paradigm is needed, in which it is encouraged to utilize model-based approaches to develop FDCs with multiple dose levels and dose ratios for exposure-based treatment that will enable personalization.

ACKNOWLEDGEMENTS

This study was performed under the umbrella of Copenhagen Centre for Regulatory Science, a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring Pharmaceuticals, LEO Pharma) as well as patient organizations (Rare Diseases Denmark). The centre is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus and the research is not company-specific product or directly company related.

COMPETING INTERESTS

A.N.-N. was funded by Novo Nordisk A/S. Novo Nordisk A/S had no role in the design or conduct of the study, collection, management, analysis or interpretation of data or in preparation of the manuscript. The other authors have no competing interests to declare.

CONTRIBUTORS

Study design: all authors. Data collection: A.N.-N. and T.M.L. Data analysis: A.N.-N., C.B.P., T.L. and T.M.L. Writing of first draft: A.N.-N. Provided critical revisions and approving the final version: all authors.

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How to cite this article: Nøhr-Nielsen A, De Bruin ML, Thomsen M, et al. Body of evidence and approaches applied in the clinical development programme of fixed-dose combinations in the European Union from 2010 to 2016. *Br J Clin Pharmacol*. 2019;85:1829–1840. https://doi.org/10.1111/bcp.13986